CANCER RESEARCH

Endocrinology

Abstract 1012: Selective estrogen receptor downregulators and immune checkpoint inhibitors in breast cancer immunotherapy

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Abstract

Breast cancers (BC) with expression of estrogen receptor-alpha (ERα) occur in more than 70% of newly-diagnosed patients in the U.S. Endocrine therapy with antiestrogens or aromatase inhibitors is an important intervention for BCs that express ERα, and it remains one of the most effective targeted treatments. However, substantial numbers of patients with localized disease, and almost all patients with metastatic BC, become resistant to current endocrine therapies. ERα is present in most resistant BCs, and in many of these its activity continues to regulate BC growth. Fulvestrant represents a class of ERα antagonists that elicit selective ER downregulation (SERDs), an action that helps overcome several resistance mechanisms. Unfortunately, full antitumor efficacy of fulvestrant is limited by its poor bioavailability in clinic. We have designed and tested a new generation of steroid-like SERDs. Using ERα-positive BC cells *in vitro*, we find that these compounds suppress ERα protein levels with efficacy similar to fulvestrant. Moreover, these new SERDs markedly inhibit ERα-positive BC cell proliferation *in vitro* even in the presence of estradiol-17β. *In vivo*, SERD-128 significantly inhibits tumor growth in MCF-7 xenograft models in a dose-dependent manner ($P<0.001$). Further, our findings show that new SERDs as well as fulvestrant *also* interact with immune cells expressing ER such as myeloid-derived suppressor cells (MDSC), dendritic cells and T-lymphocytes. Importantly, MDSCs act to protect tumors from immune recognition and elimination *in vivo*. Since a fraction of triple-negative breast cancers (TNBC; ERα-/PR-/HER2-) but not other BC subtypes respond to immune checkpoint inihbitors (ICIs), we assessed the antitumor effects of SERDs in murine TNBCs in immune-competent, syngeneic mouse models. Notably, SERD treatment induced a blockade of MDSC populations in tumors and rendered TNBCs *in vivo* more susceptible to ICIs, thereby leading to enhanced tumor killing. Since monotherapy with checkpoint inhibitors has not been effective for most TNBCs, combination therapies with SERDs that enhance immune recognition may increase immunotherapy responses in TNBC and improve patient survival. In addition, SERDs combined with ICIs may potentially benefit patients with other BC subtypes that are unresponsive to current endocrine treatment strategies. [Funded by Tower Cancer Research Foundation-Jessica M. Berman Fund, NCI U54 CA-14393 and UCLA Innovation Fund].

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